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10/594,177	08/13/2007	Andreas Ehlich	2590.0050002/EJH/SAC	5698

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WASHINGTON, DC 20005

EXAMINER

HIRIYANNA, KELAGINAMANE T

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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03/30/2011

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/594,177	Applicant(s) EHLICH, ANDREAS	
	Examiner KELAGINAMANE T. HIRIYANNA	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 January 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4,6-47 and 49-53 is/are pending in the application.
- 4a) Of the above claim(s) 10,13-47 and 49-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4,6-9,11 and 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>01/13/2010</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response of 01/13/2011 to office action mailed on 10/13/2010 is entered.

Claims 1 & 4 are amended.

Claims 10, 13-47 and 49-53 are withdrawn.

Claims 2, 3, 5, 48, and 54 are cancelled.

Claims 1, 4, 6-9 and 11-12 are pending and presently under examination.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300**.*

Withdrawn: Claims 1-8 and 11 rejections under 102(b) as being anticipated by Goldspink et al., (US 2003/0008836 A1) for the reasons of record as set forth in the Office Action mailed on 10/13/2010 is withdrawn in view of Applicants amendments to the cited claims.

Withdrawn: Claims 1-9 and 11 & 12 rejections under 35 USC 103 (a) as being unpatentable over Wobus et al (1997 J. Mol. Cell. cardiol. 29:1525-1539) in view of Benkel et al (WO 98/49320) for the reasons of record as set forth in the Office Action mailed on 10/13/2010 is withdrawn in view of Applicants arguments and in view of a revised rejection below.

Withdrawn: Double Patenting Warning for the reasons of record as set forth in the Office Action mailed on 10/13/2010 is withdrawn in view of Applicants amendments and cancellations to the cited claims.

Withdrawn: Objection to specification for the reasons of record as set forth in the Office Action mailed on 10/13/2010 is withdrawn in view of Applicants filing of revised paragraph including the PCT filing.

Withdrawn: Written description rejection under 35 U.S.C. 112, first paragraph for the reasons of record as set forth in the Office Action mailed on 10/13/2010 is withdrawn in view of Applicants arguments and amendments to the cited claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 4, 6-9 and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite as it recites "cells are derived from embryonic stem cells" as a limitation. All cells in an organism are derived from embryonic stem cells and hence it duplicates claim 1.

Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1, 4, 6-9 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of monitoring differentiation of stem cell into specific cell lineage by measuring the amount of secreted activity of a reporter gene product by the differentiated cell wherein said gene expressed in the differentiating cell under the control of an operatively linked to a promoter, is not enabled for any construct of reporter gene without an operatively linked promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of invention as claimed encompasses monitoring differentiation of cells containing any recombinant nucleic acid molecule comprising a reporter gene linked operatively to a cell type-specific regulatory sequence but with or without an operatively linked promoter for expressing said reporter.

The specification at best teaches only teaches the expression of a gene encoding a secreted reporter gene product SEAP under the control of a promoter of a mouse alpha-

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myosin gene and does not teach any reporter gene without a promoter that is being expressed. The art at the time of invention only teaches expression of a (reporter) gene requires an operatively linked promoter sequence.

Since the specification fails to disclose enabled examples of gene constructs that encompass the scope and breadth of instant claims, it would be undue experimentation to one of skill in the art to determine whether any reporter gene could be expressed in a differentiating cell without an operatively linked gene promoter sequence. Art teaches away from such constructs. The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation. At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 6-9 and 11-12 are rejected under 102(b) as being anticipated by Benkel et al (WO 98/49320).

The above claims are drawn to a method of monitoring cell differentiation comprising steps of culturing cells capable of differentiating wherein said cells contain at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation and at least one cell type-specific

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regulatory sequence operably linked to said reporter gene or maintaining a non human animal comprising said cells under conditions allowing differentiation and determining the amount of activity of the reporter gene product in the culture medium or in the body fluid and wherein said reporter gene product comprises a secretory leader sequence and the secreted reporter gene product is not recaptured from said body fluid or cell culture medium.

WO 98/49320 teaches the advantages of using a reporter gene system for studying the regulation of gene expression that is of fundamental importance among others to cell division and cell differentiation. Further towards this goal WO 98/49320 teaches reporter genes whose expression product is secretable for monitoring the same (entire article; abstract). WO 98/49320 teaches that there are several secretable reporter systems that including a secreted alkaline phosphatase (SEAP), alpha-amylase, hGH etc (p.1-2) and further exemplifies the use of a secretable alpha-amylase gene with a signal peptide coding region and tissue of cell type specific promoters and the measurement of the secreted product is simple, quantitative, sensitive safe, inexpensive and superior to other secretable reporters as the range of available variants of alpha-amylase allows the assays to be performed in virtually any host without any interference i.e., non recaptured after secretion and fully available for assay (entire article; p.1-3; p.6-9). The cited art thus clearly anticipates the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4, 6-9 and 11-12 are rejected under 35 USC 103 (a) as being unpatentable over Benkel et al (WO 98/49320; art of record) in view of Goldspink et al., (US 2003/0008836 A1; art of record) and Bronstein et al., (1994, Biotechniques 17: 172-177; art of record)

The above claims are drawn to a method of monitoring cell differentiation comprising steps of culturing cells capable of differentiating wherein said cells contain at

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least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation and at least one cell type-specific regulatory sequence operably linked to said reporter gene or maintaining a non human animal comprising said cells under conditions allowing differentiation and determining the amount of activity of the reporter gene product in the culture medium or in the body fluid and wherein said reporter gene product comprises a secretory leader sequence and the secreted reporter gene product is not recaptured from said body fluid or cell culture medium. .

Benkel (WO 98/49320) teaches the advantages of using a reporter gene system for studying the regulation of gene expression that is of fundamental importance among others to cell division and cell differentiation. Further towards this goal WO 98/49320 teaches reporter genes whose expression product is secretable for monitoring the same (entire article; abstract). WO 98/49320 teaches that there are several secretable reporter systems that including a secreted alkaline phosphatase (SEAP), alpha-amylase, hGH etc (p.1-2) and further exemplifies the use of a secretable alpha-amylase gene with a signal peptide coding region and tissue of cell type specific promoters and the measurement of the secreted product is simple, quantitative, sensitive safe, inexpensive and superior to other secretable reporters as the range of available variants of alpha-amylase allows the assays to be performed in virtually any host without any interference i.e., non recaptured after secretion and fully available for assay (entire article; p.1-3; p.6-9).

Regarding claims Goldspink clearly teaches a method of detecting myoblast differentiation by transfecting recombinant nucleic acid molecules encoding a human alpha-gal reporter gene under the control of promoter comprising MLC1/3 enhancer to undifferentiated myoblasts wherein the reporter gene was expressed and secreted from differentiated muscle cell in vitro culture (entire article; abstract; specifically paragraphs (0052-0059).

Bornstein teaches improvements in the detection sensitivity of SEAP reporter using chemiluminiscent assays of the secreted reporter from cells in culture or tissue (entire article; abstract).

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Thus it would have been obvious for one of ordinary skill in the art to incorporate SEAP reporter gene of Benkel for lacZ gene in the reporter construct of Goldspink and follow the differentiation of stem cells to specific tissue types or cell types using very sensitive SEAP assays taught by Bornstein. One of ordinary skill in the art would have been motivated to make and use of an assayable secreted reporter that will not be captured by tissues or the cells for monitoring a gene regulation during differentiation of a cell into tissue cell type as it is less invasive and avoids lysis of the cells. One of ordinary skill in the art would have reasonable expectation of success making using recombinant progenitor or stem cell having a reporter gene construct that codes for a secretable reporter protein for evaluating and identifying the differentiated cells as the art teaches that it is routine to use a recombinant secretable reporter for marking differentiation. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.*, whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR)

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system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/ROBERT M KELLY/

Primary Examiner, Art Unit 1633